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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,560	02/22/2000	Kenneth Iain Cumming	9701-6	3011

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	
MAIL DATE	DELIVERY MODE
05/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/510,560	CUMMING ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *258-345* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 265,267,273,274,277,280-282,288,290,291,293,294,301,304,305,307,308,315,319,321,327,328,331,333,335,336 and 341.

Continuation of Disposition of Claims: Claims rejected are 258-264,266,268-272,275,276,278,279,283-287,289,292,295-300,302,303,306,309-314,316-318,320,322-326,329,330,332,334,337-340 and 342-345 and 269-272, 287, 323-326, 337, 342 and 343.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A Request for Continued Examination under 37 CFR § 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on March 5, 2009, has been entered.

Status of the Claims

Claims 258-345 are pending in the instant application; claims 265, 267, 273, 274, 277, 280, 281, 282, 288, 290, 291, 293, 294, 301, 304, 305, 307, 308, 315, 319, 321, 327, 328, 331, 333, 335, 336 and 341 are withdrawn from consideration; claims 258-264, 266, 268-272, 275, 276, 278-279, 283-287, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322-326, 329, 330, 332, 334, 337-340, 342-344 and 345, are the subject of the Office Action below. Note: claims 269-272, 287, 323-326, 337, 342 and 343 have been reintroduce into prosecution (*i.e.*, the bisphosphonate claims).

Claim Rejections - 35 USC § 103 – Maintained in part

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295, 296, 302, 303, 306, 309, 310, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345, are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts *et al.*, International Patent Application Publication WO 97/05903, published on February 20, 1997, in view of Heiber *et al.*, U.S. Patent No. 5,346,701, issued on September 13, 1994, and optionally any one or more of the following of: Teng *et al.*, U.S. Patent No. 6,747,014 B2, issued on June 8, 2004; Garces *et al.*, U.S. Patent No. 5,736,161, April 7, 1998; and Bachynsky *et al.*, U.S. Patent No. 5,190,748, issued on March 2, 1998, is maintained in part (*i.e.*, maintained on claims that read on all compounds other than bisphosphonates), and further supported by Sawada *et al.*, *Pharmaceutical Research*, *8(11)*:1365-1371 (**1991**).

Applicants allege that the rejection is improper because the Watts requires multiple absorption promoters or an absorption promoter and a dispersing agent (page 15). Applicants assert that Watts is so narrowly focused that Watts does not appreciate the effects that a promoter, such as sodium caprate, can have on its own.

This is incorrect as Watts clearly recognizes the effects of sodium caprate as an absorption promoter.

Applicants also allege that their claimed invention is not directed to a formulation having a two-component absorption promoter. This is simply incorrect as Applicants claims read on "one or more absorption enhancers" (see claim 258).

However, the Examiner agrees that in view of the Applicants' declaration that the rejection is not applicable to the claims that are directed to formulations comprising bisphosphonate drugs (*i.e.*, claims 269-272, 287, 323-326, 337, 342 and 343).

Regarding the other data provide in the declaration, the current claims are broader than that of the data, and does not overcome the combined teachings in the art for the reasons stated below.

Reiterated Rejection:

Claim 258 is directed towards a solid oral dosage form which is effective in delivering a drug and an enhancer, each as defined below, to an intestine and which comprises a pharmaceutical composition consisting of:

(A) a therapeutically effective amount of a hydrophilic or macromolecular drug in the form of crystalline and/or amorphous particles;

(B) one or more absorption enhancers, each of which: (i) is a solid at room temperature; (ii) is a salt of a medium chain fatty acid having a carbon length of form 8 to 14 carbon atoms in particulate form; and (iii) is present in the dosage form in a therapeutically effective amount and such that the ratio of the drug to the one or more absorption enhancers is 1:100,000 to 10:1; and

(C) one or more excipients selected from the group consisting of rate-controlling polymeric materials, diluents, lubricants, disintegrants, plasticizers, anti-tack agents, opacifying agents, pigments, and flavorings.

Watts discloses a drug delivery composition (tablet, capsule, including a gelatin capsule, and a pellet) for drug delivery through oral administration (see Abstract; accordingly this is a delayed release formulation) comprising a drug (*e.g.*, oligosaccharide or polysaccharide including low molecular weight heparin (meets the drug limitations of claims 258, 262-264, 266, 275, 276, 289, 302, 316, 317, 318, 320, 329, 330, 334, 338, 339, 340, 344 and 345); see page 8), and an absorption promoter (see page 24; see also Example 10 on page 22 of the PCT). This formulation is a solid at room temperature, as is the enhancer sodium caprate. It is also provided with the auxiliary excipient Labrasol, and without Labrasol, which instead of being an enhancer is considered a dispersing agent (see Detailed Description, see also Example 1-3 on pages 16-18). Watts also teaches the use of a single enhancer with insulin and capric acid (see Figure 3, and description thereof). Watts teaches that the absorption promoter comprises a fatty acid or a salt thereof, where the fatty acid has between 6 and 16 carbon atoms, for example capric acid (Example 10) or its sodium salt, sodium caprate (pages 5, 24; see also claims 1 and 3) which can be used *alone* (meets teaching of claimed limitation of sodium caprate in claims 258, 262, 268, 278, 279, 302, 316, 322, 332, 334 and 340) or in admixture with a fatty acid derivative. For example, Watts states regarding the use of sodium caprate on intestinal absorption of active compounds that are otherwise not readily bioavailable:

> "***It has been known for some time that sodium caprate can act as an absorption promoting agent***, probably by the perturbation of membranes or modification of tight junctions between cells (Kajii et al. J. Pharm. Sci. 77 390, 1988)."

Watts, paragraph bridging pages 2 and 3 (emphasis added).

Watts further teaches that the drug can be chosen from LMWH, and more (pages 8, 11-12, and 24; and claim 6). Watts teaches that the composition is formulated in a capsule (*e.g.*, hard/soft gelatin), tablet (as in claims 260), pellet, or multiparticulate capsule or tablet which is comprised of or coated with a material which is dissolved by the conditions found in the intestines such as "rate-controlling" for enteric release, and comprises a cellulose ester, HPMC at page 9, lines 14-29 (as in claim), or a methacrylic acid polymer at pages 10-12 (as in claims 259, 261, 283, 284), for *in vivo* therapeutic administration to a patient (see pages 14-15). Such enteric coatings meet the claimed enteric coatings (compare to paragraph 0037 of Applicants' disclosure, *i.e.*, "releases the drug and the enhancer *rapidly* once the *appropriate* site in the intestine has been reached" as in claim 283). Watts teaches sodium caprate and capric acid; both components prepared in a formulation similar to Example 3 would result in all components being a solid at room temperature.

Although Watts teaches tablet dosage forms as well as preparing certain formulations by adding certain mass amounts of active and enhancer, Watts does not explicitly state that the active agent or the enhancer are provided in the form of particles.

Heiber teaches certain formulations that are pressed into tablet form from a dry blend of LMWH and an enhancer (*i.e.*, NaTC):

> "LMWH tablets are prepared in the following manner. ***An active LMWH layer was prepared by dry blending 2.010 g LMWH***, 0.504 g of hydroxypropyl cellulose, (KLUCEL LF) ***and 0.450 g of NaTC***. To this was added 500 µl of 200 proof ethanol and the mixture was wet blended to give a wet granulation having a dough like consistency. The wet granulation was passed through an 18 mesh screen and allowed to dry for 3 hours in a draft oven at 25 °C. The dried granulation was then passed through a 20 mesh screen and placed in a glass vial with 0.030 g of magnesium stearate and 0.006 g of mint flavor and dry blended again. A 100 mg amount of this mixture was filled into a 1/2" diameter die and ***precompressed*** on a Carver Press Model C ***with 0.25 ton pressure*** for a 3 second time dwell time to form the active drug/enhancer/polymer layer."

Heiber, col. 10, lines 25-41. Such a teaching meets the physical form limitations of the independent claims as well as claims 285, 286, and 303. As in claims 292, 295, 296, 306, 309 and 310, Heiber teaches the inert diluent sorbitol (col. 10, lines 42-45).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts and Heiber are directed toward providing pharmaceutical dosage forms, such as tablets, for administering pharmaceutically active peptides that have poor absorption characteristics. Watts clearly shows that an oral dosage form comprising insulin has a much increased bioavailability in the presence of the caprate anion in the GIT, and suggests a number of active peptides that this approach is useful for, including LMWH in the form of a tablet, and specifically with sodium caprate as the enhancer. Heiber teaches a particular tablet formulation that is prepared as a dry blend of LMWH and enhancer particles and is compressed to have a particular tablet shape and size. Although Watts does not explicitly teach a dry blend compression tablet, and Heiber does not teach sodium caprate, arriving at an oral tablet for GIT delivery in the claimed physical form would have been obvious in view Watts and Heiber because the differences between what is claimed and what is taught by Watts and Heiber is considered well-known in the art and/or routine. For example, see Teng, where a pharmaceutical composition of a pressed tablet is prepared from a powder composition of particles comprising sodium caprylate used as an enhancer for improved absorption of an active agent (*i.e.*, an oligonucleotide; Example 15). See Garces, wherein an oral capsule is prepared with LMWH and sodium caprate, and therefore has increased absorption (Example 2), and Sawada, each of who demonstrate the understanding the sodium caprate enhances absorption of the claimed compounds through mucous membrane tissues. Bachynsky further demonstrates these points, as it is taught that the active agents may take the form of the a liquid formulation or numerous solid formulations:

> "The formulation can be filled into a hard- or soft-shell capsule or, if the formulation is a liquid, absorbed onto a suitable carrier to ***make a free flowing powder*** and then filled into the capsule or, alternatively, ***compressed into a pill or tablet***. Still other possible dosage forms include microcapsule or beadlet forms of the antibacterial compound mixed with the absorption enhancing system which may thereafter be encapsulated in an enteric coated capsule.

> ***Usage of enteric coating materials in this manner serves to protect the antibacterial compound from the gastric fluid and to achieve optimum delivery of the antibacterial compound together with the absorption enhancing system to the intestine***. The enteric coating material is, for the most part, resistant to the gastric fluid and is unaffected by it but dissolves in the intestinal fluid to cause release of the drug."

Bachynsky, col. 8, lines 18-50; multiple approaches for delivery through various mucosal membranes, such as oral or rectal administration are also disclosed.

Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 258-264, 266, 268, 275, 276, 278-279, 283-286, 289, 292, 295-300, 302, 303, 306, 309, 310-314, 316-318, 320, 322, 329, 330, 332, 334, 338-340, 344 and 345, are rejected under 35 U.S.C. 103(a), as being unpatentable over Watts *et al.*, International Patent Application Publication WO 97/05903, published on February 20, 1997, in view of Heiber *et al.*, U.S. Patent No. 5,346,701, issued on September 13, 1994, and optionally any one or more of the following of: Teng *et al.*, U.S. Patent No. 6,747,014 B2, issued on June 8, 2004; Garces *et al.*, U.S. Patent No. 5,736,161, April 7, 1998; Bachynsky *et al.*, U.S. Patent No. 5,190,748, issued on March 2, 1998; Sawada *et al.*, *Pharmaceutical Research*, *8(11)*:1365-1371 (**1991**), as applied to the listed claims in the rejection above, and further in view of Burk *et al.*, U.S. Patent No. 5,221,734, issued on June 22, 1993.

The limitations of the previously rejected claims and the corresponding teachings of the art is found in the rejection above, and hereby incorporated into the instant rejection.

None of Watts or Heiber explicitly teach the claimed stearic acid lubricant or crospovidone, as in claims 297-300 and 311-314.

Burk teaches certain pharmaceutical compositions for delivering a particular growth factor (i.e., milk growth factor), and discloses tablet formulation and their common excipients. Included in the description are the lubricant stearic acid and the disintegrant crospovidone (col. 11, lines 28-58).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Watts, Heiber and Burk are directed towards

the delivery active agents using tablet formulations. Where Watts and Heiber teach certain oral formulations comprising an enhancer and LMWH, and teach tablet formulations, neither reference provides an exhaustive list of common excipients in standard tablet cores containing the active ingredients. However, the claimed compositions directed towards the stearic acid lubricant and disintegrant crospovidone, as taught by Burk, are common and well-known excipients for standard/instant release tablets, having predictable results that are commensurate in scope with the claims (e.g., tablet, or an enterically coated tablet). Therefore, the invention as a whole was *prima facie* obvious at the time it claimed.

Double Patenting

Claims 258, 302, 269-272, 287, 323-326, 334, 337, 340, 342 and 343 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of the claims of copending Application No. 11/400,689 and 11/733,007. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 258, 302, 269-272, 287, 323-326, 334, 337, 340, 342 and 343 are directed to the same invention as that of the claims of commonly assigned 11/733,007. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Conclusions

No claim is allowable.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639